A-Bomb Data: Detection of Bias in the Life Span Study Cohort

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By drawing a distinction between A-bomb survivors with and without bomb-related injuries, it was possible to see that instead of the Life Span Study (LSS) cohort being a normal, homogenous population, there were significant differences between survivors with and without multiple injuries, and that these differences occurred largely among survivors who were under 10 or over 50 years of age when exposed. There also was a concentration of A-bomb-related injuries among survivors who eventually developed leukemia. So it is possible that deaths before 1950 had left the LSS cohort permanently biased in favor of persons who had high levels of resistance to all (early and late) effects of radiation. It is also possible that the high proportion of leukemia cases among the deaths of A-bomb survivors from 1950 to 1970 were because the radiation caused an initial leukocytosis followed by loss of immunologic competence. — *Environ Health Perspect* 105(Suppl 6):1519–1521 (1997)

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Introduction

In spite of the huge population losses sustained by Hiroshima and Nagasaki, Japan, between August 1945 and October 1950, the noncancer death rate of the Life Span Study (LSS) cohort remained close to expectations based on national statistics and (unlike the cancer death rate) did not exhibit evidence of a linear trend with dose (*1*). As a result of these observations "the use of A-bomb data for risk assessment is generally predicated on the assumption that the survivors, apart from their radiation dose, are representative human beings" (*2*).

According to this hypothesis, cancer was the only late effect of the A-bomb radiation and neither division of the exposed population into deaths before and after 1950 nor division of the LSS cohort into survivors with and without bomb-related injuries would have affected levels of sensitivity to this late effect of the radiation (current hypothesis, Figure 1). There are, however, several analyses of LSS data by Stewart and Kneale (*3–5*) that are difficult to reconcile either with the assumption of no selection effects of the early deaths or with that of no late effects of the radiation apart from cancer.

Though lacking full access to all the records assembled by the Radiation Effects Research Foundation (RERF), Stewart and Kneale have a diskette version of LSS data (RERF, Hiroshima, Japan) and observed that, first, for all causes of noncancer deaths except cardiovascular accidents there is a biphasic dose–response curve whose lowest point is close to 1 Gy (*3*). Second, the proportion of high-dose (over 1 Gy) survivors is much smaller for the youngest and oldest of five exposure age groups (under age 10 or over age 50) than for intervening age groups (*4*). Third, for survivors with two or more bomb-related injuries, the dose–response curve for leukemia and other neoplasms is exceptionally steep and this finding is true primarily for those exposed before age 10 or after age 50 (*5*).

On the strength of these observations Stewart and Kneale came to two conclusions. First, compared with other A-bomb victims, persons who died before 1950 as well as survivors with bomb-related injuries were exceptionally sensitive to all (early and late) effects of radiation (alternative hypothesis, Figure 1). Second, the relatively high levels of sensitivity to cancer effects of radiation regularly observed by the RERF among persons who were under 30 years of age

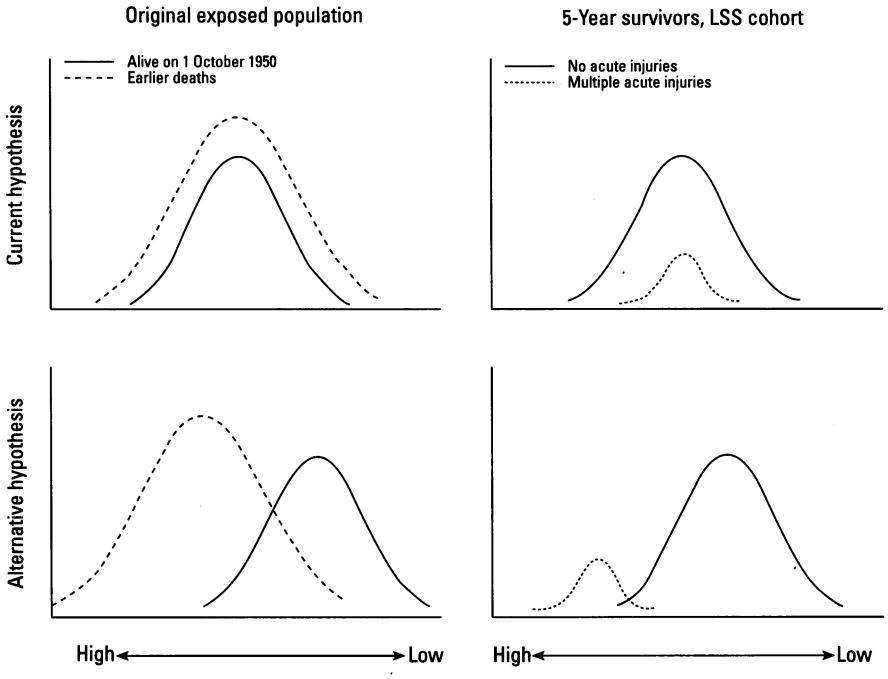

Figure 1. Levels of sensitivity to cancer effects of radiation.

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Abbreviations used: Gy, gray; LSS, Life Span Study; RERF, Radiation Effects Research Foundation.

when exposed (*6*) probably were the result of older persons succumbing more often to acute effects of high doses of radiation.

If these conclusions are true, it may one day be necessary to replace the current hypothesis depicted in Figure 1 with the alternative hypothesis. Such a change would have important implications for risk assessment. The latest analysis of LSS data by Stewart and Kneale (*5*) is briefly summarized below with regard to the 5965 deaths from neoplasms during the 1950 to 1985 period.

Materials and Methods

Stewart and Kneale began with the same sample of LSS data as the Biological Effects of Ionizing Radiation V committee (*7*); they also used the same tests (Poisson regression analysis) of dose-related effects for cancer and other causes of death. Instead of assuming that the cohort of 75,991 survivors was a single homogeneous population, however, they restricted their analysis to 74,042 survivors who had records of bomb-related injuries (Tables 1 and 2) and observed the effects of treating these survivors by considering the survivors either as a single cohort or as a mixture of two or three distinct cohorts (Table 3). Stewart and Kneale also followed tests of dose-related effects of the radiation (Table 4) by chi-square tests of exposure age effects and cohort homogeneity (Table 5).

Results

Regression analysis of the six cohorts listed in Table 3 yielded both evidence of a dose-related cancer risk and evidence that this risk was *a*) influenced by age when exposed to the radiation, and *b*) appreciably smaller for the 64,758 survivors who had no bomb-related injuries than for the 2601 survivors with multiple injuries. Because in this respect the small group had more in common with the nonsurvivors than the large group, it is possible that the usual source of risk estimates for cancer effects of radiation (i.e., the LSS cohort of A-bomb survivors) is biased in favor of persons who had exceptionally high levels of resistance to late as well as early effects of radiation (alternative hypothesis, Figure 1).

Discussion

By showing that the normal noncancer death rate of the LSS cohort was associated with two dose-related factors, Stewart and Kneale's analysis (*3*) identified both a reason why the usual effect of an excessively high death rate (i.e., a reduced death rate caused by survival of the fittest) was not a feature of LSS data, and a reason why the death rate for blood diseases other than leukemia remained both higher than normal and strongly dose related long after 1950 (residual effect of the marrow damage that caused thousands of deaths from aplastic anemia before 1950). Then came the 1993 analysis of RERF publications as well as LSS data (*4*) with evidence that there was a conspicuous shortage of first trimester exposures in the cohort formed from live births between August 1945 and June 1946 (the *in utero* cohort). The analysis also established that there was a shortage of high doses (over 1 Gy) in the LSS cohort among persons who were under 10 or over 50 years of age when exposed. Four years later these findings were followed by an analysis of bomb-related injuries (*5*) that by showing that one requirement of the alternative hypothesis in Figure 1 could be met suggested that deaths before 1950 left the

Table 1. Bomb-related injuries as claimed by members of the LSS cohort when interviewed about exposure positions.

Bomb-related injuries	Claimants, no
Type	
Burns	5551 (1193)[a]
Spontaneous bleeding	3613 (2168)
Oropharyngeal lesions	2443 (1780)
Epilation	1308 (1091)
Frequency	
No data	1949[b]
0	64,758
1	6683
2	1737
3	708
4	156
Total	75,991[c]

[a]Figures in parentheses are persons with more than one type of injury. [b]There were no data for 1949 individuals; they are excluded from later tables. [c]Data from the National Academy of Sciences, National Research Council, Committee on the Biological Effects of Ionizing Radiation (BEIR V) (*7*).

Table 2. Other specifications of bomb-related injuries in the LSS cohort (excluding 1949 survivors with no records).

Specifications	Bomb-related injuries, no				Survivors, %[a]
	0	1	Multiple	Total	
Stated cause of death					
Leukemia	129	31	41	201	35.8
Other neoplasms	4855	601	308	5764	15.8
Cardiovascular	9330	984	362	10,676	12.6
Other deaths	9172	956	361	10,489	12.6
All causes of death	23,486	2572	1072	27,130	13.4
Age at exposure, years					
0–4	8756	482	95	9333	6.2
5–19	18,323	1984	761	21,068	13.0
20–34	12,507	1481	688	14,676	14.8
35–49	14,756	1739	783	17,278	14.6
50–59	6506	689	201	7396	12.0
60+	3910	308	73	4291	8.9
DS86 dose, mGy					
0–4	31,820	1253	147	3320	4.2
5–94	25,044	2231	408	27,683	9.5
95–494	7039	2367	691	10,097	30.4
495–994	665	562	725	1942	65.8
995–1994	117	158	360	635	81.6
1995+	73	122	270	465	84.3
Total (surviving and deceased)	64,758	6683	2601	74,042	12.5

DS86, the third estimate of dose for A-bomb survivors (1986). [a]With injuries.

Table 3. Classification of the study cohort by the frequency of bomb-related injuries.

Subgroups of the LSS cohort	Survivors, no	Number of deaths from	
		All causes	Neoplasms
A, all members with injury data	74,042	27,130	5965
B, denied all four injuries	63,072	22,807	4832
C, A–B	10,970	4323	1133
D, multiple injuries claimed	2601	1072	359
E, A–D	71,441	26,058	5616
F, A–(B+D)	8369	3251	784

Subgroup A of LSS cohort = B+C or D+E or B+D+F.

Table 4. Poisson regression analysis of all fatal neoplasms with chi-square tests of radiation effects.

Subgroups of the LSS cohort[a]	Excess relative risk at 1 Gy, exposure age in years							Chi squares[b]	
	Under 10	10–19	20–34	35–44	45–54	Over 55	All ages	Series I, 2 df	Series II, 7 df
A	3.02	0.74	0.35	0.32	0.12	0.01	0.48	44.4*	68.7*
B	3.48	0.87	0.76	0.44	0.13	4.44	0.77	48.8*	67.8*
C	1.19	0.38	0.11	0.27	–0.14	0.52	0.14	6.2	21.1*
D	922.9	–0.14	0.22	0.43	–0.02	5.54	0.26	7.2	20.1*
E	2.97	0.83	0.63	1.07	1.33	2.11	1.10	44.8*	54.2
F	0.54	0.90	–0.00	0.15	–0.07	0.34	0.12	2.5	10.4

df, degrees of freedom. [a]See Table 3 for explanation of cohort subgroups. [b]Chi squares: series I, constant age effect; series II, variable age effect. *$p > 0.05$.

survivors biased in favor of persons who were exceptionally resistant to all causes of death, including radiogenic cancers.

These analyses, therefore, suggest the following conclusions:

- Although some members of the LSS cohort may still be experiencing infection sensitivity effects of marrow damage, others may outlive their nonexposed contemporaries (healthy survivor effect of deaths before 1950).
- The exceptionally high frequency of bomb-related injuries among persons who eventually developed leukemia (Table 2) possibly was the result of the radiation initially causing both a leukocytosis and loss of immunologic competence, then these early changes leading to extra deaths from cases of myeloid leukemia with exceptionally short latent periods (*8*). Under this assumption the special leukemogenic effect observed in A-bomb survivors and radiotherapy patients (*9*) would have no counterpart in the exclusively low-dose situations resulting from either background radiation or occupational exposures to gamma radiation (*10*).
- Whether or not it becomes necessary to replace the current hypothesis with the alternative hypothesis (Figure 1), it would be interesting to observe the effects of adding to the data collected by the RERF other records of A-bomb survivors (from their special hospitals and clinics) and using the pooled data to study factors associated with different levels of sensitivity to the carcinogenic effects of radiation.

Table 5. Chi-square tests of exposure age effects and cohort homogeneity.

Tests	Cohort subgroups[b]	Chi squares[a] Series I, 2 df	Series II, 7 df	Series I and II differences, 5 df
Exposure age effects	A	44.4	68.7	24.3*
	B	48.8	67.8	19.0*
	C	6.2	21.1	14.9*
	D	7.2	20.1	13.7
	E	44.8	54.2	9.4
	F	2.5	10.4	7.9
				Differences between subgroup A and equivalent groups
Cohort heterogeneity	A	44.4	68.7	Series I, 5 df: Series II, 10 df
	B+C	55.0	88.9	10.6: 20.2*
	D+E	52.0	74.3	7.6: 5.6
	B+D+F	58.5	98.3	14.1*: 29.6*

[a]Chi squares: series I, constant age effect; series II, variable age effect. [b]See Table 3 for explanation of cohort subgroups. Equivalents of subgroup A of LSS cohort include: subgroups B+C, D+E, or B+D+F. *$p < 0.05$.

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